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In the Supreme Court of the United States

OCTOBER TERM, 1988

G & W LABORATORIES, INC., PETITIONER

v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

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16 pp

QUESTION PRESENTED

Whether proof that a drug is generally recognized by experts as safe and effective for its intended use under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), and therefore may be marketed in interstate commerce without the prior approval of the Food and Drug Administration, must be based on adequate, well-controlled, and published clinical studies of either (1) the drug itself, or (2) another drug for which there are such clinical efficacy studies and for which there are adequate, scientific, and published studies showing that it is a bioequivalent to the drug in question.

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OPINIONS BELOW

The order of the court of appeals (Pet. App. 1a-2a) is reported at 857 F.2d 1466 (Table). The opinion of the district court (Pet. App. 3a-19a) is unreported.

JURISDICTION

The judgment of the court of appeals was entered on August 2, 1988. A petition for rehearing was denied on September 7, 1988. The petition for a writ of certiorari was filed on October 14, 1988. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. To prevent the marketing of drugs that have not been proved safe and effective, Congress enacted the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. (& Supp. IV) 301 *et seq.*, which establishes a system of premarketing clearance for drugs. The FDCA prohibits the introduction into interstate commerce of any "new drug" unless a new drug application has been approved by the Food and Drug Administration (FDA). 21 U.S.C. (& Supp. IV) 355(a). Under the FDCA, a "new drug" includes all drugs other than those falling within certain limited exceptions. 21 U.S.C. 321(p). To obtain the FDA's approval, a drug manufacturer must prove, based on scientific evidence, including adequate well-controlled clinical studies, that a drug is safe and effective for its intended use. 21 U.S.C. (& Supp. IV) 355; see *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973).

A drug is not considered a "new drug," and thus is exempt from the premarketing approval requirement, if it is "generally recognized, among experts qualified by scientific training and expertise to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 321(p) (the general recognition exception). In *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *supra*, this Court held that a drug cannot be marketed under that exception unless its safety and effectiveness are supported by the same type of scientific evidence necessary to obtain the FDA's approval under 21 U.S.C. (& Supp. IV) 355 to market a new drug. 412 U.S. at 632.

When the drug product is claimed to be a generic copy of one already approved by the FDA, the sponsor may file

with the FDA an "abbreviated new drug application" (ANDA), which relies on the established safety and effectiveness of the previously approved drug. The FDA will approve an ANDA where the generic drug is shown to be the therapeutic equivalent of the approved pioneer drug, and therefore is safe and effective in accordance with 21 U.S.C. (& Supp. IV) 355(d). *Premo Pharmaceutical Laboratories, Inc.* v. *United States,* 629 F.2d 795, 799 (2d Cir. 1980). Therapeutic equivalence is shown by bioequivalence. 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv). Bioequivalence, in turn, is the ability of two different drug products to deliver the same active ingredients to the site at which the drug is to have its effect, at the same rate and to the same extent. 21 U.S.C. (Supp. IV) 355(j)(7)(B); *Premo,* 629 F.2d at 799 n.4. See also Pet. App. 9a.

2. In the early 1980's, petitioner introduced its prescription drug Anucort Hemorrhoidal Suppositories (Anucort) onto the market. Pet. App. 3a.[1] Petitioner did not seek the FDA's approval for that drug, nor has petitioner ever conducted and published any study of Anucort showing that it is safe and effective for its intended use, or that it is the bioequivalent of another drug that has been demonstrated to be safe and effective.

In November 1985, the government brought this in rem action under 21 U.S.C. 334 to seize a quantity of Anucort, on the ground that it was an unapproved new drug and therefore cannot be marketed in interstate commerce. The

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[1] Anucort contains (among other ingredients) hydrocortisone acetate, a steroid. It is a prescription drug because it is not safe for use except under the supervision of a licensed practitioner. See 21 U.S.C. 353(b)(1)(B). Petitioner marketed another product before 1980 that petitioner claimed was the same drug as Anucort, but petitioner offered no evidence that its earlier product had the same ingredients as Anucort, or that it was labeled for the same uses. Pet. App. 16a-17a.

government moved for summary judgment based on evidence that no adequate, well-controlled, and published clinical investigations had been performed on Anucort, and that there was no published evidence that Anucort was bioequivalent to another drug for which such studies existed.[2] The government argued that, absent such evidence, Anucort could not be generally recognized as safe or effective under 21 U.S.C. 321(p). In response, petitioner submitted affidavits from experts attesting to the safety and effectiveness of Anucort. Petitioner's experts, however, did not base their conclusions on published clinical studies of Anucort. Instead, petitioner's experts relied on studies that had been conducted on other products also containing steroids as active ingredients. None of these experts addressed the issue whether Anucort was shown to be bioequivalent to the drugs on which the experts based their conclusions. Pet. App. 3a-5a.

The district court granted the government's motion for summary judgment. Pet. App. 3a-19a. The court agreed with the FDA that Anucort could not fit within the general recognition exception unless adequate, well-controlled, and published clinical studies on Anucort established its efficacy or unless there were published studies showing that Anucort is bioequivalent to another product for which there are such clinical efficacy studies. *Id.* at 9a-10a. Since petitioner had presented no evidence to rebut the FDA's showing that no such clinical efficacy or bio-

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[2] The government also moved for summary judgment on the alternative ground that there is no consensus of expert opinion on the question whether Anucort is safe and effective. See *United States* v. *Atropine Sulfate 1.0 Mg. (Article of Drug) Dey-Dose*, 843 F.2d 860, 862 (5th Cir. 1988) (*Dey*) (describing the two-step showing necessary to prove that a drug is not a new drug). The district court, however, did not address that issue.

equivalency studies on Anucort existed, the court granted summary judgment for the agency. *Id.* at 10a-14a.

3. The court of appeals summarily affirmed the district court's decision. Pet. App. 1a-2a.

ARGUMENT

The courts below correctly held that Anucort cannot be marketed under the general recognition exception of 21 U.S.C. 321(p) in the absence of adequate and well-controlled studies establishing the effectiveness of that drug, or, at a minimum, scientific evidence that Anucort is the bioequivalent of another drug product for which such clinical efficacy studies exist. Because the court of appeals' decision is correct and does not conflict with any decision of this Court or of another court of appeals, review by this Court is not warranted.

1. The gravamen of petitioner's argument (Pet. 16-18) is that the issue whether a drug is generally recognized as safe and effective is inherently a factual, not a legal, question. Petitioner contends that the district court erred both in deferring to the FDA's judgment about the type of evidence that is necessary to establish safety and efficacy, and in failing to consider the opinions of petitioner's experts that Anucort is safe and effective. And petitioner claims that, even though its experts relied on studies showing only that one of the active ingredients in Anucort, but not Anucort itself, is safe and effective, and did not rely on clinical studies showing that Anucort is bioequivalent to another drug of proven safety and effectiveness, petitioner was entitled to a trial on the merits of its claim that Anucort is generally recognized as safe and effective. That argument lacks merit, for several reasons.

In *Hynson,* this Court ruled that 21 U.S.C. (& Supp. IV) 321(p) and 355 must be interpreted consistently and re-

quire the same type of proof that a drug is safe and effective before it can be marketed in interstate commerce, whether the drug is approved by the FDA or is shown to be exempt under the general recognition exception. The Court therefore concluded that "a drug can be 'generally recognized' by experts as effective for intended use within the meaning of the Act only when that expert consensus is founded upon 'substantial evidence' as defined in [Section 355(d)]." 412 U.S. at 632. And in *United States* v. *Generix Drug Corp.*, 460 U.S. 453 (1983), this Court held that the "drug" that must be generally recognized as safe and effective under 21 U.S.C. 321(p) is the entire product itself, not just its active ingredients. That is because the effects of a drug product cannot be predicted from its active ingredients alone. For example, inactive ingredients added to bind the product (known as "excipients") may affect the rate at which the active ingredients are delivered to a diseased organ and thereby affect the safety or efficacy of the entire drug product. *Generix*, 460 U.S. at 455; *Premo*, 629 F.2d at 799.

It follows from *Hynson* and *Generix* that the clinical studies establishing safety and effectiveness must relate to the product, and not just its active ingredients. The FDA has accordingly concluded that the requirement in 21 U.S.C. (& Supp. IV) 355(d) of studies from which "it could fairly and responsibly be concluded" that a drug is effective means that there must be published clinical efficacy studies on the product itself, or, at a minimum, published clinical efficacy studies of another drug combined with published scientific evidence that the studied drug is bioequivalent to the drug sought to be marketed.[3]

[3] The FDA argued below that all bioequivalence determinations should be left to the agency, which has the expertise to make that determination, rather than the courts. The district court held that if general recognition of Anucort is to be based on its bioequivalence to another drug product, that recognition must be based on adequate,

Congress has confirmed the FDA's interpretation of Section 355(d) in the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585. That Act established an abbreviated approval mechanism for the generic counterparts of drugs that have already been found to be safe and effective by the FDA. To obtain the FDA's approval of a generic drug under that mechanism based on the generic drug's similarity to an already approved drug, rather than on adequate and well-controlled studies submitted by the generic applicant, the Act requires the manufacturer of the drug to show that its generic drug is the bioequivalent of the approved drug. 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv); see *Denial of Citizen Petition No. 85P-0421/CP (F.D.A. Sept. 29, 1986)*, slip op. 3 (ruling that new Section 355(j)(2)(A)(iv) requires "that everyone who wishes to market a generic drug submit evidence to the agency, as part of an ANDA, that the generic drug is bioequivalent to the pioneer").[4] Congress also made clear in the 1984 amendments that the generic drug manufacturer must bear the burden of showing in all cases that its drug is the bioequivalent of an approved drug, and that the FDA is not required to prove the contrary. 21 U.S.C. (Supp. IV) 355(j)(3)(F).[5]

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well-controlled, and published studies demonstrating bioequivalence. Pet. App. 9a-10a. Since petitioner's experts did not base their analysis of Anucort on any published assessment of its bioequivalence with another drug product, this case does not provide an opportunity to resolve the question whether a district court should ever undertake to determine itself whether one drug is the generally recognized bioequivalent of another.

[4] We have filed a copy of that decision with the Clerk and have provided a copy to counsel for petitioner. The only exception to that requirement involves the substitution of one active ingredient in a drug product containing more than one active ingredient. That exception, however, is not applicable here.

[5] This Court in *Generix* did not decide whether the FDA must bear the burden of going forward to show a need for bioequivalence. 460

Furthermore, it is well settled that when the question is whether a drug is generally recognized as safe and effective, the FDA does not bear the burden of showing that the drug is in fact unsafe or ineffective. The only question for a court to decide is whether the drug is generally recognized as safe and effective based on published studies, and not whether it is safe and effective in fact. See, *e.g.*, *United States* v. *Undetermined Quantities of Various Articles of Drug*, 675 F.2d 994, 999-1001 (8th Cir. 1982), cert. denied, 460 U.S. 1051 (1983); *Premo*, 629 F.2d at 803-804; *United States* v. *1,048,000 Capsules, More or Less, Afrodex*, 494 F.2d 1158, 1160 (5th Cir. 1974); *Tyler Pharmacal Distributors, Inc.* v. *HEW*, 408 F.2d 95, 99 (7th Cir. 1969). The same rule should apply when the question is whether one drug is the bioequivalent of another drug of proven safety and effectiveness. In this context, the only question for a court to decide, as the Second Circuit held in *Premo*, 629 F.2d at 803-804, is whether the drug at issue is generally recognized, based on published studies, as the bioequivalent of the comparison drug, not whether the drug at issue is a bioequivalent in fact.

Finally, the FDA's interpretation of the substantial evidence requirement in Section 355(d) is also supported by important policy concerns. Just as the determination whether a drug is effective cannot rest on the knowledge and experience of individual physicians (see *Hynson*, 412 U.S. at 619 (footnote omitted) ("The hearings underlying that 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.")), neither can it rest on unverified assumptions that drug products with the same active ingredients

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U.S. at 461 n.12. Congress, however, has answered that question in the 1984 amendments by requiring the manufacturer to establish bioequivalence. Petitioner therefore errs in stating (Pet. 21-23) that this case provides an appropriate vehicle to answer the question left open in *Generix*.

will have the same effects. Because of the limited resources available to the FDA, saddling the FDA with the burden of demonstrating the absence of bioequivalence for the thousands of generic drugs on the market would seriously impair the agency's ability to safeguard the public health. By contrast, it is eminently sensible to require a drug manufacturer to establish that its product is the bioequivalent of another product which it claims to be the therapeutic equivalent, since the manufacturer is the party exposing the public to the product.

In sum, the courts below correctly concluded that petitioner was required to show, based on published studies, and not just the opinions of its own experts, that Anucort is generally recognized as the bioequivalent of a drug of proven safety and effectiveness. Because petitioner offered no such evidence, the district court correctly entered judgment in the agency's favor.

2. Petitioner also contends (Pet. 8-19) that the FDA has taken inconsistent positions on the question presented by this case. In support of this argument, petitioner relies on an FDA regulation, 21 C.F.R. 320.22(b)(2), and two Federal Register notices citing that regulation, 49 Fed. Reg. 11888 (1984), and 53 Fed. Reg. 30756 (Aug. 15, 1988). None of those materials, however, supports petitioner's claim.

The regulation and 1984 Federal Register notice only state that, under certain circumstances, the FDA may waive its general policy of requiring that bioequivalence be shown by an in vivo study and may instead accept some other proof of bioequivalence. See *Dey*, 843 F.2d at 863.[6]

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[6] See 21 C.F.R. 320.22(b) (the FDA "shall waive the requirements for the submission of *evidence obtained in vivo*" in certain specified circumstances) (emphasis added). The 1984 Federal Register notice also refers to the waiver of only in vivo studies.

The FDA's regulations authorize the agency to accept other types of bioequivalence analyses. 21 C.F.R. 320.53. The FDA has concluded

The regulation and notice do not state that the FDA can or will waive the statutory requirement that a drug manufacturer establish bioequivalence in some manner, and the 1984 amendments do not permit the FDA to waive that requirement. *Denial of Citizen Petition,* slip op. 3.[7]

Moreover, neither the regulation nor the 1984 Federal Register notice applies to a drug like Anucort. The regulation allows the FDA to waive the in vivo study requirement only for a "topically applied preparation, e.g., a cream, ointment or gel, intended for local therapeutic effect." 21 C.F.R. 320.22(b)(2). Anucort cannot qualify under that regulation, since it is undisputed (and petitioner concedes, Pet. 2) that Anucort is a suppository that is applied internally to the rectum, even though it is labeled for use in connection with external conditions. The regulation, however, refers to a drug that is applied directly to the site at which the drug is to have its effect, such as an antibiotic ointment that is applied directly to a wound, which does not include Anucort.[8]

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that, rather than rely on in vivo testing of the final product, the agency can in some limited classes of cases rely on product formulation and chemistry and the manufacturing process, which are the primary factors affecting bioequivalence. See *United States* v. *Premo Pharmaceutical Laboratories, Inc.,* 511 F. Supp. 958, 980-985 (D.N.J. 1981). The 1988 Federal Register notice cited by petitioner makes that point. It states that the FDA "will address product bioavailability in the context of the monograph [proposed rule] requirements of (1) appropriate vehicles and other inactive ingredients and (2) compliance with appropriate good manufacturing practices." 53 Fed. Reg. 30776 (Aug. 15, 1988).

[7] Even if the regulation and notices permitted a drug manufacturer to show that its product is generally recognized as safe and effective based on scientific studies other than in vivo studies, petitioner still could not prevail, because it is undisputed that there are no published bioequivalence assessments of any kind involving Anucort.

[8] The FDA's interpretation of its regulation is consistent with the position that the agency took in the 1988 Federal Register notice on

Petitioner's reliance on the 1988 Notice of Proposed Rulemaking is also misplaced. That proposed rule addresses a limited class of over-the-counter drug products that are deemed by FDA to be generally recognized as safe and effective within the meaning of Section 321(p). 53 Fed. Reg. 30756. Anucort is a prescription drug (page 3 note 1, *supra*), not an over-the-counter product, and therefore would not be affected by the new rule. Moreover, the proposed rule specifically excludes rectal suppositories that, like Anucort, are offered for external uses.

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products like Anucort (53 Fed. Reg. 30773 (Aug. 15, 1988)):

> The comment is correct in stating that the Panel did not recommend labeling for the intrarectal application of suppositories and ointments containing a local anesthetic to relieve pain stemming from irriation outside the rectum (i.e., in the anal canal below the mucocutaneous junction and perianal area). Although the comment contends that such an intrarectal application would be effective because of liquefaction of the product and subsequent seepage through the anal canal, the Panel considered seepage only within the context of an incontinent anal sphincter and not within the context that an incontinent anal sphincter would provide a means to relieve external symptoms on the skin of the perianal area and the anal canal. Rather, the Panel considered intrarectal application only for local effect inside the rectum. The comment provided no data to alter the Panel's recommendations, and the agency believes that the intrarectal application of a suppository or ointment is not an appropriate means to alleviate external symptoms through liquefaction and seepage.

There is thus no merit to petitioner's argument that the FDA's construction of its own regulation is not entitled to deference since that position was first adopted during the course of this case. And even if the issue had only emerged in this case, it is not clear that FDA's construction should be entitled to no deference. See *United States* v. *Morton*, 467 U.S. 822, 835-836 n.21 (1984) ("Litigation often brings to light latent ambiguities or unanswered questions that might not otherwise be apparent."); *Gardebring* v. *Jenkins*, No. 86-978 (Apr. 19, 1988), slip op. 13-14.

Finally, the proposed rule does not apply to products, like Anucort, that contain steroids as active ingredients.

3. Contrary to petitioner's contention (Pet. 19-21), *Premo Pharmaceutical Laboratories, Inc.* v. *United States, supra,* does not conflict with the decision below. *Premo* flatly rejected the drug manufacturer's claim that a district court, when determining whether a drug is generally recognized as safe and effective under Section 321(p), may decide whether the drug is in fact safe and effective for its intended use based on its bioequivalence to another drug. The Second Circuit held that the only question for a court to decide is whether published scientific data, including any bioequivalency studies, establish a consensus that the drug is generally recognized as safe and effective. 629 F.2d at 803-804. *Premo* therefore firmly supports the conclusion that the only question before the district court in this case was whether published scientific data showed that Anucort was the bioequivalent of another drug of proven safety and effectiveness, and that the district court was not authorized to make the bioequivalence determination as a question of fact. Since that is precisely what petitioner sought to do in this case, *Premo* supports the court of appeals' decision.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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